FORM PTO-1390 (REV 10-95)

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: MERCK 2370

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 10/031367

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP00/06464 | 7 JULY 2000 | 22 JULY 1999 |

TITLE OF INVENTION: N-(INDOLCARBONYL-)PIPERAZIN DERIVATIONS

APPLICANT(S) FOR DO/EO/US: BOTTCHERK, Hennning, et al

**Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:**

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ have been transmitted by the International Bureau
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

**Items 11. to 16. below concern document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

| U.S. APPLICATION NO (if known, see 37 CFR §1 5) | INTERNATIONAL APPLICATION NO | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 10/031367 | | |

17. ☒ The following fees are submitted:

**BASIC NATIONAL FEE ( 37 CFR §1.492 (a) (1) - (5)):**

| | | CALCULATIONS PTO USE ONLY |
|---|---|---|
| Search Report has been prepared by the EPO or JPO..... | $890.00 | |
| International preliminary examination fee paid to USPTO (37 CFR §1.482)..... | $710.00 | |
| No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... | $740.00 | |
| Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... | $1040.00 | |
| International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... | $100.00 | |

| | | |
|---|---|---|
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $890.00 | |
| Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F R. §1.492(e)). | | |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 7 - 20 = | 0 | x $ 18.00 | $0.00 | |
| Independent claims | 1 - 3 = | 0 | x $ 84.00 | $0.00 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | + $ 280.00 | | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $890.00 | |
| Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be | | | | | |
| **SUBTOTAL =** | | | | $890.00 | |
| Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)). | | | | | |
| **TOTAL NATIONAL FEE =** | | | | $890.00 | |
| Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R §§3.28, 3.31). $40.00 per property. | | | | | |
| **TOTAL FEES ENCLOSED =** | | | | $890.00 | |
| | | | | Amount to be refunded: | |
| | | | | charged: | |

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO. Customer Number 23,599

23599
PATENT TRADEMARK OFFICE

SIGNATURE

Anthony J. Zelano
NAME

27,969
REGISTRATION NUMBER

Filed: 18 JANUARY 2002
AJZ:kmo

**IN THE UNITED STATES DESIGNATED/ELECTED OFFICE**

| | | |
|---|---|---|
| International Application No. | : | PCT/EP00/06464 |
| International Filing Date | : | 7 JULY 2000 |
| Priority Date(s) Claimed | : | 22 JULY 1999 |
| Applicant(s) (DO/EO/US) | : | BOTTCHER, Henning, et al. |

Title: N-(INDOLCARBONYL-)PIPERAZIN DERIVATIONS

**PRELIMINARY AMENDMENT**

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, applicants request the original claims be examined even though the claims were amended during the international phase.

Respectfully submitted,

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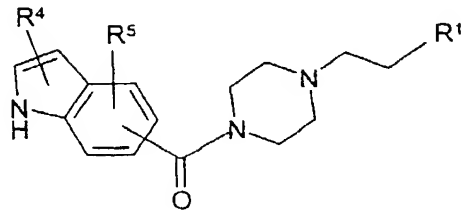
# Patent Claims

1. Compounds of the formula I



I

in which

$R^1$ is a phenyl or naphthyl radical which is unsubstituted or substituted by $R^2$ and/or $R^3$
or is $Het^1$,

$R^2$, $R^3$ in each case independently of one another are Hal, A, OA, OH or CN,

$R^4$, $R^5$ in each case independently of one another are H, CN, acyl, Hal, A, OA, OH, $CONH_2$, CONHA or $CONA_2$,

$R^4$ and $R^5$ together are also alkylene having 3-5 C atoms,

$Het^1$ is a mono- or binuclear unsaturated heterocyclic ring system, which is unsubstituted or mono- or disubstituted by Hal, A, OA or OH and contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

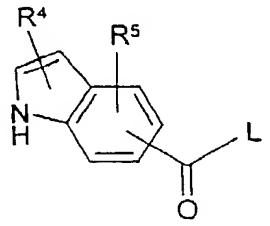
and where the indole ring can also be replaced an isatin unit,

and their physiologically acceptable salts and solvates,

(1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded.

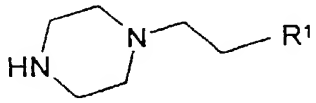
2. Process for the preparation of compounds of the formula I according to Claim 1, (1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded, characterized in that

a) a compound of the formula II



II

in which L is Cl, Br, I or a free or reactive functionally modified OH group,
and $R^4$ and $R^5$ have the meaning indicated in Claim 1,
is reacted with a compound of the formula III

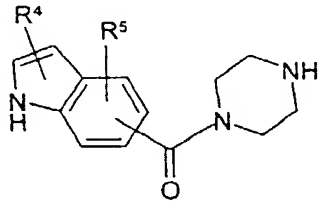


III

in which $R^1$ has the meaning indicated in Claim 1,

or

b) a compound of the formula IV



IV

in which $R^4$ and $R^5$ have the meaning indicated in Claim 1,
is reacted with a compound of the formula V

$$L\text{-}CH_2\text{-}CH_2\text{-}R^1 \qquad V$$

in which L is Cl, Br, I or a free or reactive functionally modified OH group, and $R^1$ has the meaning indicated in Claim 1,

or

c) if appropriate, one of the radicals $R^1$, $R^4$ and/or $R^5$ is converted into another radical $R^1$, $R^4$ and/or $R^5$ by cleaving, for example, an OA group with formation of an OH group and/or converting a CHO group into a CN group,

and/or
a base of the formula I which is obtained is converted into one of its salts by treating with an acid.

3. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments, (1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded.

4. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments having $5\text{-}HT_{2A}$ receptor-antagonistic action.

5. Medicaments according to Claim 4 for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

6. Pharmaceutical preparation, comprising at least one medicament according to Claim 5, and also, if

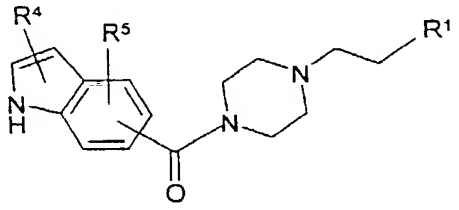
appropriate, vehicles and/or excipients and, if appropriate, other active compounds.

7. Use of compounds according to Claim 1 and/or of their physiologically acceptable salts and solvates for the production of a medicament having $5\text{-}HT_{2A}$ receptor-antagonistic action.

8. Use according to Claim 7 for the production of a medicament for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

# N-(Indolecarbonyl)piperazine derivatives

The invention relates to compounds of the formula I



I

in which

$R^1$ is a phenyl or naphthyl radical which is unsubstituted or substituted by $R^2$ and/or $R^3$ or is $Het^1$,

$R^2$, $R^3$ in each case independently of one another are Hal, A, OA, OH or CN,

$R^4$, $R^5$ in each case independently of one another are H, CN, acyl, Hal, A, OA, OH, $CONH_2$, CONHA or $CONA_2$,

$R^4$ and $R^5$ together are also alkylene having 3-5 C atoms,

$Het^1$ is a mono- or binuclear unsaturated heterocyclic ring system, which is unsubstituted or mono- or disubstituted by Hal, A, OA or OH and contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

and where the indole ring can also be replaced by an isatin unit,

and their physiologically acceptable salts and solvates,

(1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded.

The invention was based on the object of finding novel compounds having valuable properties, in particular

those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their physiologically acceptable salts and solvates have valuable pharmacological properties together with good tolerability, as they have actions on the central nervous system. The compounds have a strong affinity for 5-$HT_{2A}$ receptors; they furthermore exhibit 5-$HT_{2A}$ receptor-antagonistic properties.

For the in-vitro detection of the affinity for 5-$HT_{2A}$ receptors, it is possible to use, for example, the following test (Example A1). The 5-$HT_{2A}$ receptors are exposed to both [$^3$H]ketanserin (a substance known for its affinity for the receptor) and the test compound. The decrease in the affinity of [$^3$H]ketanserin for the receptor is a sign of the affinity of the test substance for the 5-$HT_{2A}$ receptor. Detection is carried out analogously to the description of J.E. Leysen et al., Molecular Pharmacology, 1982, 21: 301-314 or as also described, for example, in EP 0320983.

The efficacy of the compounds according to the invention as 5-$HT_{2A}$ receptor antagonists can be measured in vitro analogously to W. Feniuk et al., Mechanisms of 5-hydroxytryptamine-induced vasoconstriction, in: The Peripheral Actions of 5-Hydroxytryptamine, ed. Fozard JR, Oxford University Press, New York, 1989, p. 110. Thus the contractility of the rat tail artery, caused by 5-hydroxytryptamine, is mediated by 5-$HT_{2A}$ receptors. For the test system, vessel rings, prepared from the ventral rat tail artery, are subjected to perfusion with an oxygen-saturated solution in an organ bath. By introduction of increasing concentrations of 5-hydroxytryptamine into the solution, a response to the cumulative concentration of 5-HT is obtained. The test compound is then added to the organ bath in suitable concentrations and a second concentration curve is

measured for 5-HT. The strength of the test compound on the shift of the 5-HT-induced concentration curve to higher 5-HT concentrations is a measure of the 5-$HT_{2A}$ receptor-antagonistic property in vitro.

The 5-$HT_{2A}$-antagonistic property can be determined in vivo analogously to M.D. Serdar et al., Psychopharmacology, 1996, 128: 198-205.

Other compounds which likewise exhibit 5-$HT_2$-antagonistic actions are described, for example, in EP 0320983.
Similar piperazine derivatives having antiarrhythmic properties are disclosed, for example, in EP 0431945. Other indolecarbonyl derivatives having analgesic properties are described in EP 0599240. WO 99/11641 describes phenylindole derivatives having 5-$HT_2$-antagonistic properties.

The compounds of the formula I are therefore suitable both in veterinary and in human medicine for the treatment of functional disorders of the central nervous system and also of inflammation. They can be used for the prophylaxis and for the control of the sequelae of cerebral infarcts (cerebral apoplexy) such as stroke and cerebral ischaemia and for the treatment of extrapyramidal motor side effects of neuroleptics and also of Parkinson's disease, for the acute and symptomatic therapy of Alzheimer's disease and the treatment of amyotrophic lateral sclerosis. They are likewise suitable as therapeutics for the treatment of brain and spinal cord traumata. In particular, however, they are suitable as pharmaceutical active compounds for anxiolytics, antidepressants, antipsychotics, neuroleptics, antihypertensives and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD; e.g. WO 9524194), anxiety states and physiological changes which accompany anxiety states such as, for example, tachycardia, tremors or sweating

(e.g. EP 319962), panic attacks, psychoses, schizophrenia, anorexia, delusional obsessions, agoraphobia, migraine, Alzheimer's disease, sleep disorders and also sleep apnoea, tardive dyskinesias, learning disorders, age-dependent memory disorders, eating disorders such as bulimia, drug abuse such as, for example, abuse of alcohol, opiates, nicotine, psychostimulants such as, for example, cocaine or amphetamines (e.g. US 6004980), sexual functional disorders, painful conditions of all kinds and fibromyalgia (e.g. WO 9946245).

The compounds of the formula (I) are suitable for the treatment of extrapyramidal side effects (EPS) in neuroleptic drug therapy. EPS is characterized by Parkinson-like syndromes, akathisia and dystonic reactions (e.g. EP 337136). They are further suitable for the treatment of nervous anorexia, angina, Reynaud's phenomenon, coronary vasospasms, in the prophylaxis of migraine (e.g. EP 208235), pain and neuralgia (e.g. EP 320983), for the treatment of the Rett syndrome with autistic traits, of the Asperger syndrome, of autism and autistic disorders, in concentration deficiencies, developmental disorders, hyperactivity states with mental underdevelopment and stereotypic behavioural states (e.g. WO 9524194).

In addition, they are suitable for the treatment of endocrine disorders such as hyperprolactinaemia, furthermore in vasospasms, thrombotic disorders (e.g. WO 9946245) hypertension and gastrointestinal disorders.

They are furthermore suitable for the treatment of cardiovascular disorders and also extrapyramidal symptoms such as described in WO 99/11641 on page 2, lines 24-30.

The compounds according to the invention are further suitable for decreasing intraocular pressure and for the treatment of glaucoma. They are also suitable in

animals for the prophylaxis and treatment of symptoms of intoxication on the administration of ergovaline. The compounds are furthermore suitable for the treatment of disorders of the cardiovascular system (WO 99/11641, page 3, lines 14-15).
The compounds according to the invention can also be employed together with other active compounds in the treatment of schizophrenia. Possible other active compounds are the compounds mentioned in WO 99/11641 on page 13, lines 20-26.

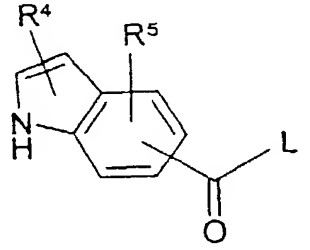
They can furthermore be employed as intermediates for the production of further pharmaceutical active compounds.

The invention relates to the N-(indolecarbonyl)-piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts. The invention also relates to the solvates, e.g. hydrates or alcoholates, of these compounds.

The invention accordingly relates to the compounds of the formula I and a process for the preparation of compounds of the formula I according to Claim 1.

The process for the preparation of compounds of the formula I according to Claim 1, (1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded, is characterized in that

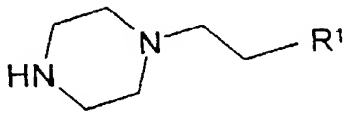
a) a compound of the formula II




II

in which L is Cl, Br, I or a free or reactive functionally modified OH group,

and $R^4$ and $R^5$ have the meaning indicated in Claim 1, is reacted with a compound of the formula III

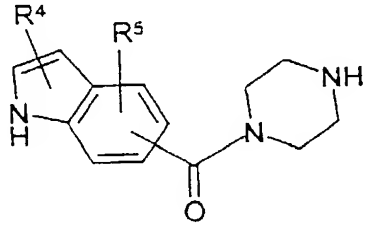


III

in which $R^1$ has the meaning indicated in Claim 1,

or

b) a compound of the formula IV



IV

in which $R^4$ and $R^5$ have the meaning indicated in Claim 1,
is reacted with a compound of the formula V

$$L\text{-}CH_2\text{-}CH_2\text{-}R^1 \qquad V$$

in which L is Cl, Br, I or a free or reactive functionally modified OH group, and $R^1$ has the meaning indicated in Claim 1,

or

c) if appropriate, one of the radicals $R^1$ , $R^4$ and/or $R^5$ is converted into another radical $R^1$, $R^4$ and/or $R^5$ by cleaving, for example, an OA group with formation of an OH group and/or converting a CHO group into a CN group,

and/or a base of the formula I which is obtained is converted into one of its salts by treating with an acid.

The invention also relates to the compounds of the formula I according to Claim 1, and to their physiologically acceptable salts and solvates as medicaments, (1*H*-indol-5-yl)-(4-phenethylpiperazin-1-yl)methanone being excluded.

The invention relates in particular to the compounds of the formula I according to Claim 1, and to their physiologically acceptable salts and solvates as medicaments having 5-$HT_{2A}$ receptor-antagonistic action.

The invention also relates to the compounds of the formula I, and their enantiomers and diastereomers, and their salts.

The indole ring can also be replaced by an isatin unit. Isatin is an isolole which is substituted by oxo in the 2- and 3-position = indole-2,3-dione.

For all radicals which occur a number of times, such as, for example, A or Hal, it holds true that their meanings are independent of one another.

The radical A is alkyl and has 1 to 6, preferably 1, 2, 3 or 4, in particular 1 or 2, C atoms. Alkyl is therefore in particular, for example, methyl, furthermore ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore trifluoromethyl or pentafluoroethyl.

Acyl preferably has 1-6 C atoms and is, for example, formyl, acetyl, propionyl, butyryl, furthermore trifluoroacetyl or pentafluoropropionyl.

Alkylene is propylene, butylene or pentylene.
OA is preferably methoxy, furthermore also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

Hal is fluorine, chlorine, bromine or iodine, in particular fluorine or chlorine.

$R^1$ is unsubstituted, preferably - as indicated - monosubstituted phenyl or naphthyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-trifluoromethoxyphenyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-difluoromethoxyphenyl, o-, m- or p-fluoromethoxyphenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-chloro-3-methyl-, 2-chloro-4-methyl-, 2-chloro-5-methyl-, 2-chloro-6-methyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-5-chloro-, 2-methyl-6-chloro-, 3-chloro-4-methyl-, 3-chloro-5-methyl- or 3-methyl-4-chlorophenyl, 2-bromo-3-methyl-, 2-bromo-4-methyl-, 2-bromo-5-methyl-, 2-bromo-6-methyl-, 2-methyl-3-bromo-, 2-methyl-4-bromo, 2-methyl-5-bromo-, 2-methyl-6-bromo-, 3-bromo-4-methyl, 3-bromo-5-methyl- or 3-methyl-4-bromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-tri-tert-butylphenyl, furthermore preferably 2-nitro-4-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, 2,5-dimethylphenyl, 2-hydroxy-3,5-dichlorophenyl, 2-fluoro-5- or 4-fluoro-3-trifluoromethylphenyl, 4-chloro-2- or 4-chloro-3-trifluoromethyl-, 2-chloro-4-

or 2-chloro-5-trifluoromethylphenyl, 4-bromo-2- or 4-bromo-3-trifluoromethylphenyl, p-iodophenyl, 2-nitro-4-methoxyphenyl, 2,5-dimethoxy-4-nitrophenyl, 2-methyl-5-nitrophenyl, 2,4-dimethyl-3-nitrophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3,5-dimethylphenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 2,4-dichloro-5-methylphenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 2-methoxy-5-methylphenyl or 2,4,6-triisopropylphenyl.

$R^1$ is also $Het^1$.

$Het^1$ is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6 or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benzo-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

$R^1$ is very particularly preferably phenyl, p-chlorophenyl, p-fluorophenyl, thiophen-2-yl, 5-chlorothiophen-2-yl, 2,5-dichlorothiophen-3-yl and 2- or 3-furyl.

$R^4$, $R^5$ are in each case independently of one another preferably H, Hal, alkyl having 1-6 C atoms, alkoxy having 1-6 C atoms or hydroxyl, furthermore cyano or acyl.

$R^4$ is preferably H, Hal, A, OA, OH, CN or acyl. $R^5$ is preferably H.

Preferred compounds of the formula I are those in which the $R^1$-$CH_2$-$CH_2$-piperazinecarbonyl radical substitutes the 4-, 5-, 6- or 7-position of the indole ring.

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to Ii, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in formula I, but in which

| | | |
|---|---|---|
| in Ia | $R^1$ | is phenyl; |
| in Ib | $R^1$ | is phenyl which is unsubstituted or monosubstituted by Hal; |
| in Ic | $R^1$ | is phenyl which is monosubstituted by Hal, or $Het^1$; |
| in Id | $R^1$ | is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$; |
| in Ie | $R^1$ | is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$, |
| | $Het^1$ | is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal or A and contains one or two identical or |

different heteroatoms such as nitrogen, oxygen and sulfur;

in If $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,
$R^4$ and $R^5$ in each case independently of one another are H, HAL or A,
$Het^1$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal or A and contains one or two identical or different heteroatoms such as nitrogen, oxygen and sulfur,

in Ig $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,
$R^4$, $R^5$ in each case independently of one another are H, Hal or A,
$R^4$ and $R^5$ together are also alkylene having 3-5 C atoms
$Het^1$ is thienyl or furyl which is unsubstituted or mono- or disubstituted by Hal or A,

in Ih $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,
$R^4$ is H, Hal, CN, acyl or A,
$R^5$ is H,
$R^4$ and $R^5$ together are also alkylene having 3-5 C atoms,
$Het^1$ is thienyl or furyl which is unsubstituted or mono- or disubstituted by Hal or A;

in Ii $R^1$ is phenyl or naphthyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,
$R^4$ is H, Hal, CN, acyl, A or $CONH_2$,
$R^5$ is H,

$R^4$ and $R^5$ together are also alkylene having 3-5 C atoms,

$Het^1$ is thienyl or furyl which is unsubstituted or mono- or disubstituted by Hal or A,

and where the indole ring can also be replaced by an isatin unit.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

If desired, the starting substances for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

In the compounds of the formulae II and V, the radical L is preferably Cl or Br; however, it can also be I, OH or otherwise preferably a reactive functionally modified OH group, in particular alkylsulfonyloxy having 1-6 (e.g. methanesulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, 1- or 2-naphthalenesulfonyloxy) or otherwise trichloromethoxy, alkoxy, such as, for example, methoxy, ethoxy, propoxy or butoxy, furthermore also phenoxy.

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

As a rule, the starting substances of the formulae II and III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

The reaction of the compounds II and III proceeds according to methods such as are known from the literature for the alkylation or acylation of amines. However, it is also possible to react the compounds in the presence of an indifferent solvent. Suitable solvents are, for example, hydrocarbons, such as benzene, toluene, xylene; ketones such as acetone, butanone; alcohols such as methanol, ethanol, isopropanol, n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; nitriles such as acetonitrile, and, if appropriate, also mixtures of these solvents with one another or mixtures with water. The addition of an acid-binding agent, for example of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of piperazine derivative of the formula II can be favourable. Depending on the conditions used, the reaction time is between a few minutes and 14 days; the reaction temperature between approximately 0 and 150°, normally between 20 and 130°.

In addition, compounds of the formula I can be prepared by reacting amines of the formula IV with a component of the formula V comprising the radical $R^1$.

As a rule, the respective components are known or can be prepared by known processes as already described.

A base of the formula I obtained can be converted into the associated acid addition salt using an acid. For this reaction, suitable acids are those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid, sulfamic acid, furthermore organic acids, specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxy-ethanesulfonic acid, benzenesulfonic acid, p-toluene-sulfonic acid, naphthalenemono- and -disulfonic acids and laurylsulfuric acid.

The free bases of the formula I can, if desired, be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide, or sodium or potassium carbonate, if no further acidic groups are present in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can likewise be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention furthermore relates to the medicaments according to the invention having 5-$HT_{2A}$ receptor-antagonistic action for the treatment of psychoses,

schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The invention also relates to a pharmaceutical preparation comprising at least one medicament according to the invention and also, if appropriate, vehicles and/or excipients and, if appropriate, other active compounds.
In this case, the medicaments can be brought into a suitable dose form together with at least one solid, liquid and/or semiliquid vehicle or excipient and, if appropriate, in combination with one or more further active compounds.

The invention furthermore relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-$HT_{2A}$ receptor-antagonistic action.

The invention also relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-$HT_{2A}$ receptor-antagonistic action for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The pharmaceutical preparations can be employed as medicaments in human and veterinary medicine. Suitable carrier substances are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilisates obtained used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or aromatizers. They can, if desired, also contain one or more further active compounds, e.g. one or more vitamins.

In this case, the substances according to the invention are as a rule administered in analogy to known preparations, preferably in doses between approximately 0.1 and 500 mg, in particular between 5 and 300 mg, per dose unit. The daily dose is preferably between approximately 0.01 and 250 mg/kg, in particular between 0.02 and 100 mg/kg, of body weight.

In this case, the substances according to the invention as a rule are preferably administered in doses of between approximately 1 and 500 mg, in particular between 5 and 100 mg per dose unit. The daily dose is

preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each intended patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

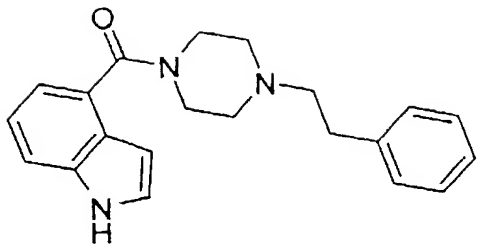
Above and below, all temperatures are indicated in °C. In the examples below, "customary working up" means: if necessary, the solvent is removed, if necessary, water is added, if necessary, the mixture is adjusted, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and concentrated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Example A1

Preparation of a suspension of 5-$HT_{2A}$ receptors:
Frontal rat cortex is homogenized in ice-cold buffer. The homogenate is centrifuged for 10 minutes at 4°C and 50,000xg. The pellet is resuspended in 2.5 ml of ice-cold tris buffer, made up with 10 ml of additional buffer and centrifuged as described above. The pellet is then resuspended in buffer and diluted to give a homogenate which contains 60 mg of material/ml.
0.1 ml of the suspension, 100 µl of a 5 nM solution of [$^3$H]ketanserin, 100 µl of a solution of the test compound (concentration in the range from $10^{-5}$ to $10^{-10}$ mol per litre) are added to the incubation tubes and made up to 1 ml with buffer. The tubes are incubated for 15 minutes at 37°C. After termination of the incubation by immersing the tubes in an ice bath, the cooled suspension is filtered through a glass filter in vacuo. The filters are washed 3 × with 5 ml of cold buffer and then transferred to scintillation tubes. The filters are analysed by means of liquid scintillation spectrometry in 8 ml of Triton X scintillator fluid.

Example 1

A solution of 2.0 g of 4-carboxyindole and 8.1 g of 2-chloro-1-methylpyridinium iodide in 60 ml of N-methylpyrrolidone (NMP) is treated with a solution of 2.36 g of 4-phenethylpiperazine and 8.2 g of ethyldi-isopropylamine (EDIPA) in 20 ml of NMP and subsequently stirred at room temperature for 3 hours. The mixture is worked up in the customary manner and the crude product is obtained. This is dissolved in acetone and the hydrochloride is precipitated using aqueous hydrochloric acid. After drying, 4.59 g of (1*H*-indol-4-yl)-(4-phenethylpiperazin-1-yl)methanone, hydrochloride, m.p. 289.3°, is obtained.



, m.p. 289.3°.

The following compounds are obtained analogously

(1*H*-indol-4-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 250°;
(1*H*-indol-4-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
(1*H*-indol-4-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
(1*H*-indol-4-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(1*H*-indol-4-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 166-168°;

(1*H*-indol-5-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone,
(1*H*-indol-5-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
(1*H*-indol-5-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
(1*H*-indol-5-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(1*H*-indol-5-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,
(3-formyl-1*H*-indol-5-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 240.9°;

(1*H*-indol-6-yl)-[4-phenethylpiperazin-1-yl)methanone,
(1*H*-indol-6-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 284.0-284.4°;

(1*H*-indol-6-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 204.2-205.7°;
(1*H*-indol-6-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 251.0-252.5°;
(1*H*-indol-6-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(1*H*-indol-6-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 240-241°;

(3-formyl-(1*H*-indol-6-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone,
(3-cyano-1*H*-indol-6-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 280°;

(1*H*-indol-7-yl)-(4-phenethylpiperazin-1-yl)methanone, hydrochloride, m.p. 221°;
(1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 274°;
(1*H*-indol-7-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
(1*H*-indol-7-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 251.0-252.5°;
(1*H*-indol-7-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(1*H*-indol-7-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,
(3-formyl-1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 287°;
(3-cyano-1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. >300°;

(2,3-dimethyl-1*H*-indol-7-yl)-(4-phenethylpiperazin-1-yl)methanone,
(2,3-dimethyl-1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, 86.5-89°;

(2,3-dimethyl-1*H*-indol-7-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
(2,3-dimethyl-1*H*-indol-7-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
(2,3-dimethyl-1*H*-indol-7-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(2,3-dimethyl-1*H*-indol-7-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,

(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-(4-phenethylpiperazin-1-yl)methanone, hydrochloride, m.p. 235-237°;
(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone,
(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
(6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,

(3-formyl-(1*H*-indol-6-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 279.3°;
(1*H*-indol-6-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 257.5-259.0°;
(1*H*-indol-4-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 266-267°;
(3-cyano-1*H*-indol-5-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 210°;
(3-cyano-1*H*-indol-7-yl)-[4-(naphth-2-ylethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 284.0-285.5°;
(3-cyano-1*H*-indol-4-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 284.0-285.5°;

(3-cyano-1*H*-indol-4-yl)-[4-(2-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 213-215.5°;
(3-cyano-1*H*-indol-7-yl)-[4-(2-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 212.5-214°;
(3-aminocarbonyl-1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 280-281°;
(3-cyano-1*H*-indol-7-yl)-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, methanesulfonate, m.p. 212.5-214°;
(3-cyano-1*H*-indol-7-yl)-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone, hydrochloride, m.p. 301.5-303.0°;
(3-cyano-1*H*-indol-7-yl)-(4-phenethyl-piperazin-1-yl)methanone, methanesulfonate, m.p. 294.7-297°;
(3-cyano-1*H*-indol-7-yl)-[4-(2,4-difluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 295.6-297.0°;
7-{4-[2-(4-fluorophenyl)ethyl]piperazin-1-carbonyl}-1*H*-indole-2,3-dione.

The following examples relate to pharmaceutical preparations:

**Example A: Injection vials**

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and aseptically sealed. Each injection vial contains 5 mg of active compound.

**Example B: Suppositories**

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

**Example C: Solution**

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \times 2\ H_2O$, 28.48 g of $NaH_2PO_4 \times 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

**Example D: Ointment**

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

**Example E: Tablets**

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

**Example F: Coated tablets**

Analogously to Example E, tablets are pressed and are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

**Example G: Capsules**

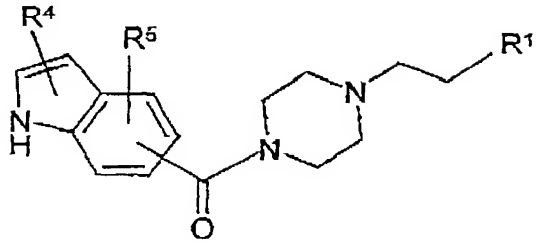
2 kg of active compound of the formula I are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

**Example H: Ampoules**

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is filled into ampoules, lyophilized under aseptic conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

## Patent Claims

1. Compounds of the formula I



I

in which

$R^1$ is a phenyl or naphthyl radical, each of which is unsubstituted or substituted by $R^2$ and/or $R^3$, or is $Het^1$,

$R^2$ and $R^3$ are each, independently of one another, Hal, A, OA, OH or CN,

$R^4$ is H, CN, acyl, Hal, A, OA, OH, $CONH_2$, CONHA or $CONA_2$,

$R^5$ is H,

$R^4$ and $R^5$ together are alternatively alkylene having 3-5 carbon atoms,

$Het^1$ is a monocyclic or bicyclic unsaturated heterocyclic ring system which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA or OH and which contains one, two or three identical or different heteroatoms, such as nitrogen, oxygen and sulfur,

A is alkyl having 1-6 carbon atoms,

Hal is F, Cl, Br or I,

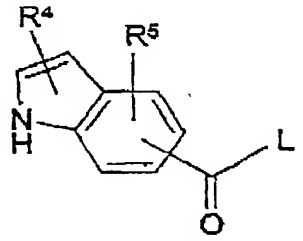
and where the indole ring may also be replaced by an isatin unit, and physiologically acceptable salts and solvates thereof,

where (1*H*-indol-5-yl)(4-phenethylpiperazin-1-yl)methanone and 1-((5-methoxy-1*H*-indol-7-yl)carbonyl)-4-(2-phenylethyl)piperazine are excluded.

2. Process for the preparation of compounds of the formula I according to Claim 1, where (1*H*-indol-5-yl)(4-phenethylpiperazin-1-yl)methanone

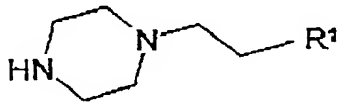
and 1-((5-methoxy-1*H*-indol-7-yl)carbonyl)-4-(2-phenylethyl)piperazine are excluded, characterised in that

a) a compound of the formula II



II

in which L is Cl, Br, I or a free or reactively functionally modified OH group,
and $R^4$ and $R^5$ are as defined in Claim 1,
is reacted with a compound of the formula III

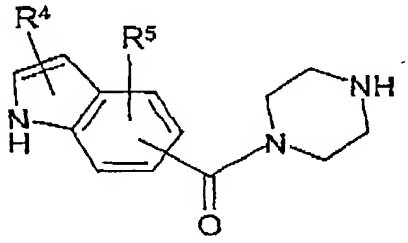


III

in which $R^1$ is as defined in Claim 1,

or

b) a compound of the formula IV



IV

in which $R^4$ and $R^5$ are as defined in Claim 1,

is reacted with a compound of the formula V

$$L\text{-}CH_2\text{-}CH_2\text{-}R^1 \qquad V$$

in which L is Cl, Br, I or a free or reactively functionally modified OH group, and $R^1$ is as defined in Claim 1,

or

c) if desired, one of the radicals $R^1$, $R^4$ and/or $R^5$ is converted into another radical $R^1$, $R^4$ and/or $R^5$ by, for example, cleaving an OA group to form an OH group and/or converting a CHO group into a CN group,

and/or
a resultant base of the formula I is converted into one of its salts by treatment with an acid.

3. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates, where (1*H*-indol-5-yl)(4-phenethylpiperazin-1-yl)methanone and 1-((5-methoxy-1*H*-indol-7-yl)carbonyl)-4-(2-phenylethyl)piperazine are excluded, as medicaments.

4. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates, as medicaments having a 5-$HT_{2A}$ receptor antagonistic action.

5. Medicament according to Claim 4 for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders, such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively influencing obsessive-compulsive disorder (OCD).

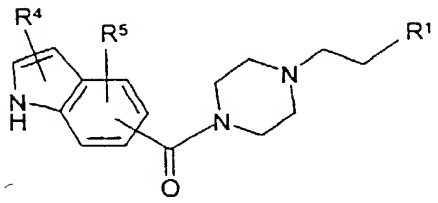
6. Pharmaceutical preparation comprising at least one medicament according to Claim 5, and, if desired, excipients and/or assistants and, if desired, other active ingredients.

7. Use of compounds according to Claim 1 and/or of physiologically acceptable salts and solvates thereof for the preparation of a medicament having a 5-$HT_{2A}$ receptor antagonistic action.

8. Use according to Claim 7 for the preparation of a medicament for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders, such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively influencing obsessive-compulsive disorder (OCD).

# Abstract

Compounds of the formula I



I

in which $R^1$, $R^2$, $R^4$ and $R^5$ have the meanings indicated in Claim 1, are potent 5-$HT_{2A}$ antagonists and are suitable for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, nervous anorexia, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

Docket No.
Merck 2370

# Declaration and Power of Attorney For Patent Application
## English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

N-(INDOLCARBONYL-)PIPERAZIN DERIVATIVES

the specification of which

(check one)

☐ is attached hereto.
☒ was filed on 07/07/2000 as United States Application No. or PCT International Application Number PCT/EP00/06464
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application(s) | | | Priority Not Claimed |
|---|---|---|---|
| 199 34 433.7 (Number) | Germany (Country) | 22.07.1999 (Day/Month/Year Filed) | ☐ |
| _____ (Number) | _____ (Country) | _____ (Day/Month/Year Filed) | ☐ |
| _____ (Number) | _____ (Country) | _____ (Day/Month/Year Filed) | ☐ |

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

| (Application Serial No.) | (Filing Date) |
|---|---|
| (Application Serial No.) | (Filing Date) |
| (Application Serial No.) | (Filing Date) |

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |
|---|---|---|
| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |
| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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1-00

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